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OCULAR REACTIONS IN ANAPHYLAXIS

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The anaphylactic state appears to concern practically every part of the body, and I have made observations especially of the anaphylactic reactions of the eye and of the structures closely associated with it. Most of the studies so far made in this respect have not been thorough enough, and in order to accomplish the purpose of my work, I limited myself to the study of the reactions of guinea-pigs to horse serum.

Schultz¹ studied the reactions of the smooth muscle of the intestine and of the blood vessels, etc., in anaphylaxis, and Dale² the reactions of the uteri muscle and the lung of guinea-pigs. These investigators observed an increased reactivity of smooth muscles in sensitized animals, which was confirmed by Friedberger and Kumagai.³ It was therefore natural to study the reactions of the smooth muscles of the eyelids and the iris, the blood vessels of the lids, the conjunctiva, the fundus and reactions of the lacrimal and Harder's glands, to the application of horse serum locally, as well as after general administration. At the same time, certain general phenomena were closely observed. I made a special effort to study the local ocular phenomena.

The animal was kept quiet in a dark room and all confusing stimulation was avoided carefully. Both eyes were illuminated symmetrically with an electric light, 40 w, 115 v, from a distance of 30 cm. in front of them. The width of the lid and of the pupil were measured by a palpebro-pupillometer that I had made, figuring 15 light and 15 dark circles of from 1.0 to 8.0 mm. in diameter, and 0.5 mm. apart, arranged in regular parallel rows, both vertical and transverse lines crossing in the center of the square of oblong quadratic side lines, the side and crossing lines being marked in millimeters. The light circles were used for the measurement of the width of the lids generally, also of the width of the pupils of the albinotic eyes; the dark circles were used for the measurement of dark pupils; the side and crossing scales served as controls. The pupils were measured after adaptation of the retina to light for 5 minutes.

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¹ Jour. Pharmacol. and Exper. Therap., 1910, 1, p. 549; Bull. Hyg. Lab., 1912, No. 80.

² Jour. Pharmacol. and Exper. Therap., 1913, 4, p. 167.

³ Ztschr. f. Immunitätsf. u. Exper. Therap., 1914, 22, p. 269.

The iris was examined by a magnifying lens under electric light and when necessary by oblique illumination.

The examination of the fundus was made by indirect and direct methods, using the De Zeng's electric ophthalmoscope.

Effect of Instillation of Normal Salt Solution into the Conjunctiva of Normal Guinea-Pig.—The animal was a white male with pink eyes; one drop of 0.9% salt solution was dropped into the left eye 3 times at intervals of 30 minutes. The results (table 1) indicate that a drop of salt solution dropped into the conjunctival sac of a normal albino guinea-pig may cause a slight contraction of the pupil (0.5 mm.). A second drop was followed by a stronger closure of the lid but without any change in the pupil, and a third drop had the same effect. In this case the closure of the lid and the contraction of the pupil were of course reflex.

TABLE 1
LID AND PUPIL REACTION TO INSTILLATION OF SALT SOLUTION

Time in Minutes	Left Eye		Right Eye (Control)	
	Lid Fissure in Mm.	Pupil in Mm.	Lid Fissure in Mm.	Pupil in Mm.
Before	6	3	6	3
After First Instillation	1	5	6	3
	4	5.5	5.5	3
	10	5	5.5	3
	12-17	5.5	5.5	3
	20	5	5.5	2.5
	25-20	6	6	3
After Second Instillation	1	2	5.5	3
	3	3	5.5	3
	5-7	3	4	3
	10-12	5	5	3
	15-19	5.5	5.5	3
	20	3.5	4	3
	22	4	4	3
	25	5	5.5	3.5
	27	5	5	3
	30	5.5	5.5	3
After Third Instillation	1	3	5.5	3.5
	3	2	5	3
	5	3	4	3
	7	5	5	3
	10	4	4	3
	12	4.5	5	3
	15	5	5	3

The Ocular Reactions of a Normal Guinea-Pig to Normal Unheated Horse Serum Dropped on the Conjunctiva.—The animal was a male, brown and white, the iris dark brown, the fundus strongly pigmented. It was kept in a dark room and the eye illuminated from the left side in this instance. When the eye had become adapted to the light, one drop of unheated normal horse serum was placed on the conjunctiva of the same eye 3 times at intervals of 30 minutes. The other eye was kept covered during this time. The results of the measurements are shown in table 2.

I have observed that the eyes of guinea-pigs do not react together, and it may not be possible to avoid certain irregularities in the results.

In this experiment the first drop of normal horse serum caused opening of the lid and dilatation of the pupil in one minute. The opening of the lid was at its maximum at first and lasted for 7 minutes. The dilatation of the pupil reached its maximum in 7 minutes and continued for about 10 minutes. The second drop of horse serum caused narrowing of the lid and increased dilatation of the pupil, the dilatation reaching its maximum in 3 minutes and continuing for 17 minutes. The third drop seemed to be without any effect. Until 2 hours later the lids and pupil of the eye experimented on remained more contracted than in the control eye.

TABLE 2
LID AND PUPIL REACTION OF NORMAL GUINEA-PIG TO NORMAL HORSE SERUM

Time in Minutes		Left Eye	
		Lid Fissure in Mm.	Pupil in Mm.
Before		5:5	3.5
After First Instillation	1-3	6	3.75
	5	6	4
	7	6	4.5
	10	5.5	4
	11	5.5	3.5
	13-17	5	3.5
	24-27	4.5	3.5
	30	5	3.5
After Second Instillation	1	4	4
	3-5	3.5	4.5
	7	4	4
	9	4	3.75
	12	4	3.75
	17	4	3.75
	25	5	3.25
	30	4	3.25
After Third Instillation	1	4	3.25
	5	3.5	4
	10-25	4	3
	30	3	3

Ocular Reactions in a Normal Albino Guinea-Pig to Unheated Normal Horse Serum.—The animal was male, wholly white; the fundus was not pigmented. One drop of normal horse serum was introduced into the left eye 3 times, the intervals being 15 and 45 minutes. In this case the response was more prompt than in the previous animal, the dilatation of the pupil reaching its maximum in 2 minutes. The second and third drops were followed by a more steady widening of the lid space and dilatation of the pupil, and this was succeeded by contraction lasting for about half an hour. This experiment shows that in the albino guinea-pig, the lid, as well as the pupil, reacts vigorously to repeated instillation of horse serum. Probably the differences between the albino and pigmented animals were partly individual and partly due to the differences in the content of pigment.

Ocular Reactions of Sensitized Guinea-Pig to Unheated Normal Horse Serum Dropped Into the Conjunctival Sac.—A male guinea-pig, practically wholly white, was injected Nov. 20 with 0.01 cc of normal horse serum subcutaneously. About 17 weeks later normal unheated horse serum, after having been warmed in the incubator, was dropped into the left eye 3 times at intervals of 30 minutes. In this test both eyes were illuminated with the same light and

in the same way. All eye phenomena and general symptoms were observed carefully. The results are given in table 4; the first drop caused an immediate opening of the lid and a vigorous dilatation of the pupil, the maximum being reached at once; 13 minutes later the lid and the pupil contracted. The second drop caused a slower but longer mydriasis, but had no effect on the width of the lid. The third drop was followed by narrowing of the lid and of the pupil. There was a noticeable congestion of the palpebral and ocular conjunctiva, of the margins of the cornea and of the iris, the lids being somewhat swollen, and the conjunctiva remarkably edematous; at the same time there was marked lacrimation. The congestion and edema began 36 minutes after the first drop and increased after each additional drop. It should be noted that a moderate congestion of the papillae also developed in the treated eye. The animal was restless and rubbed its nose; there were abundant fecal and urinary discharges. It is therefore evident that in this case the instillation of horse serum into the conjunctiva of a sensitized guinea-pig gave rise to both local and general anaphylactic reactions. About 4 hours after the first drop of horse serum was put in the eye, 6 c c of horse serum was injected into the peritoneal cavity and the eye and other reactions observed in the same way as before for about 37 minutes. For about 8 minutes the animal was quiet, his head reclining to the left, both eyes being watery, especially the left; in 13 minutes, he scratched his nose continually; in 14 minutes, there was a whitish discharge from both eyes, more marked in the left; in 15 minutes, the rectal temperature was 39.8 C. and respiratory frequency increased; in 17 minutes, there was circumcorneal injection, especially marked in left eye, and the body muscles were feeble; after 20 minutes the animal fell suddenly; he had convulsions of the forelegs and both eyes opened to 6 mm.; both pupils dilated to 4.5 mm.; in 23 minutes, both forelegs went through violent scatching movements; after 25 minutes the animal became quiet, lying on the belly; micturition; in 27 minutes lid fissures were 5.5 mm., pupils 3.5 mm.; in 30 minutes, the fundi were a little congested, but no hemorrhage; in 35 minutes, rectal temperature was 39.4 C.; he was a little dyspneic and at times had clonic convulsions; in 37 minutes the animal arose; the width of both lids was 5.0 mm., of both pupils 2.5 mm.; circumcorneal injections, chemosis and lacrimation appeared.

The animal was chloroformed; both lids closed, respiration ceased; he had clonic spasms; the lids were 3.0 mm. in width, the pupils 3.5 mm. in 6 minutes; death occurred in 8 minutes; the width of the lids was 4 mm., of the pupils, 5.5 mm.

After death the brain and spinal cord were markedly congested, also the mucous membranes of the eye and nose; the lungs were somewhat distended, with a few hemorrhage spots; liver, spleen and intestines were congested; other organs were normal.

Reactions to Heated Normal Horse Serum Dropped Into the Conjunctival Sac of a Sensitized Guinea-Pig.—The animal was a wholly white male; there was no pigment in the fundus. It was sensitized by subcutaneous injection of 0.01 c c of normal horse serum heated at 56 C. for 30 minutes and tested 110 days later by dropping one drop into the left conjunctival sac. The serum was warmed in the incubator before being placed in the eye, which was done 3 times, one drop at a time, with an interval of one hour between the first and second time and 30 minutes between the second and third time. After observing the changes in the eyes, 6 c c of heated serum were injected intraperitoneally, and the animal was killed with chloroform (table 5).

There was a slight contraction of the lids and of the pupil immediately after the instillation of the heated serum, probably due to reflex action; from 11 to

TABLE 3
LID AND PUPIL REACTION TO NORMAL HORSE SERUM IN A NORMAL ALBINO GUINEA-PIG

Time in Minutes		Left Eye		Right Eye (Control)	
		Lid Fissure in Mm.	Pupil in Mm.	Lid Fissure in Mm.	Pupil in Mm.
Before		5	3	5	3
After First Instillation	2	6	4	..	..
	5	6.5	3	..	..
	7	7	3	..	..
	10	5	3	5	3
After Second Instillation	15	5.75	3.75	5.5	3.5
	17	5	4.5	4	3.5
	22	4.25	4	4	3.5
	27	5	3	4.5	2.5
	35	5.5	4	5	3.5
	40	6	4	5.5	3.5
After Third Instillation	3	6	4.5	5.5	3.5
	5	5	4.5	5	3.5
	10	4.5	4.5	5	4
	17	5.5	4.5	5.5	4
	25	5.5	4.5	5.5	4.5
	30	6	5	5	4
	45	4.75	4	4.5	3.5
	60	5	4	5	3.75

TABLE 4
LID AND PUPIL REACTION OF A SENSITIZED GUINEA-PIG TO NORMAL HORSE SERUM INSTILLED IN EYE

Time in Minutes		Left Eye (Instilled)		Right Eye (Control)		Remarks
		Lid Fissure in Mm.	Pupil in Mm.	Lid Fissure in Mm.	Pupil in Mm.	
Before		4	2.5	4	2.5	
After First Instillation	1.5	5.5	4.5	5	3	Excited, scratching
	3	5	3	5	2.5	
	5	5	2.5	5	2.5	Left eyelids and conjunctive congested and swollen, circumcorneal injection and hypersecretion
	7	5	2.5	5	2.5	
	10	5	3	5	4	
	13	3.5	2	4	2.5	
	15	3	2	3	2	
	20	5	4	5	4	
	25	4.5	3	4.5	3	
	30	3	2.5	3	2.5	
	37	5	3	5	3	
After Second Instillation	3	4	3.5	4	3	Left external congestion and chemosis increased; iris and optic disk congested
	5-7	4	4	4	2.5	
	10	5	3.5	4	3	
	15	4	2.5	4	2.5	
	20-30	4	2.5	4	3	
After Third Instillation	2	3	2	4	2.5	
	5	2	2	4	2.5	
	10	4	2	4	2	
	15	5	2.5	5	2.5	
	25	4	2.5	4	?	
	30	4	2.5	4	2.5	

20 minutes later widening of the lid and dilatation of the pupil began, the conjunctiva being greatly congested; undoubtedly this action was due to the effect of the horse serum. After the second and third instillations the course of events was more rapid and associated with general excitement. There was congestion of the lid, the conjunctiva, the iris and the ear lobe as early as 7 minutes after the first instillation; later there was congestion of the disk and the retinal vessels of the treated eye, renewed after each instillation, with hypersecretion of tears beginning 22 minutes after the first instillation. At the same time there were dyspnea, excitement, and increased reflex action. After death there was marked congestion of the central nervous system with many small points of hemorrhage, also congestion of the mucous membranes; there was a hemorrhagic spot on the upper part of Tenon's capsule and hemorrhages about the entrance of the short ciliary arteries and the retinal vessels; there were also many subpleural hemorrhages, with congestion of the liver and other abdominal organs except the kidneys. After intraperitoneal injection of 6 cc of heated horse serum the congestion and edema of the lid and conjunctiva and the congestion of the iris and fundus, as well as the hypersecretion of tears, increased; there was also dilatation of the lid fissure and the pupil, but these were perhaps due more to the generous nervous stimulation.

TABLE 5
LID AND PUPIL REACTION OF SENSITIZED GUINEA-PIG TO INSTILLATION OF HEATED HORSE SERUM IN EYE

Time in Minutes	Left Eye (Instilled)		Right Eye (Control)		Remarks
	Lid Fissure in Mm.	Pupil in Mm.	Lid Fissure in Mm.	Pupil in Mm.	
Before	4	2.5	4	2.5	
After First Instillation	2	3.5	2	3.5	Left eye and earlobes congested. Left external congestion, chemosis and epiphora; iris hyperemia and congestion of optic disk
	3	4	2	3.5	
	7	3	2	3.5	
	11	6.5	4.5	6	
	15	4	3.5	4	
	20-22	4	3	3	
	24	5	3	4	
	30	4	2	4	
	40	2.5	2	3	
	50	3	2.5	4	
	60	3.5	3	4	
After Second Instillation	3	3	2	3.5	
	10	3	2	3	
	15	4.5	3.5	4	
	25	3	2.5	3	
	30	4	2.5	4	
After Third Instillation	3	3	2.5	3	Nose scratching
	7	2.5	2	3	
	10	6	2.5	6	
	15	4	3	4	
	20	2.5	2.5	2	
	30	2.5	2	3	

The Effect of Intraorbital Injection of Salt Solution Into Normal Guinea-Pigs.—Two-tenths of 2 cc of 0.9% salt solution was injected into the tissues of the left orbit of a female albino guinea-pig (table 6). This resulted in some contraction of the lids of both eyes and dilatation of the pupil of the injected eye occurring about half a minute after the injection; otherwise there were no special changes except a slight conjunctival injection and a little excess of tear

secretion. It would seem that the injection of this amount of salt solution into the orbit does not produce any special changes or reaction if made skilfully.

The Injection of Unheated Normal Horse Serum Into the Orbit of the Normal Guinea-Pig.—Two-tenths cc of unheated horse serum was injected carefully into the left orbit of a male albino. Immediately after the injection there were a slight contraction of the eyelids and moderate mydriasis of the left eye, followed by widening of the lids and an increased dilatation of the pupil lasting for one and a half hours and undoubtedly due to the stimulation of the serum of the corresponding smooth muscles. Within 3 minutes after the injection there was congestion of the injected eye with swelling of the lid and conjunctiva and increased lacrimation, these phenomena reaching their climax in 10 to 20 minutes, when the lids became everted, the discharge of tears very copious and congestion of the eyelids noted. About one hour after the injection there were only traces of inflammatory symptoms. It is interesting to note that the horse serum had a stimulating action on both lacrimal and harderian glands, due in some degree no doubt to the hyperemia.

TABLE 6
RESULTS OF INJECTION OF NORMAL HORSE SERUM INTO ORBIT IN NORMAL GUINEA-PIG

Time in Minutes	Lid and Pupil, Widths in Mm.		Remarks
	Left Eye	Right Eye (Control)	
Before injection	6.5 - 2.5	6.5 - 2.5	
After injection			
0.5	6 - 4	6 - 3.5	
1.5	6 - 3	6 - 2.5	
3	6 - 2.5	5 - 2.5	
5	5 - 3	5 - 2.5	
7	5.5 - 3	5 - 2.5	
10	7 - 3.5	6 - 3	
15-25	6.5 - 3	5 - 3	Left eye: Slight pericorneal injection Conjunctival congestion, scratching of nose, tremors
30	6 - 3	5 - 2.5	Conjunctival discharge
35	6 - 3.5	5 - 2.5	Eversion of lid, chemosis
40	5.5 - 3.5	5 - 2.5	
50	7 - 3.5	5 - 2.5	
60	7 - 3	4.5 - 2.5	
70	6 - 3	5 - 2.5	Changes in left eye diminishing, fundus normal

The Injection of Heated Normal Horse Serum Into the Orbit of the Normal Guinea-Pig.—Two-tenths cc of normal horse serum, heated to 56 C. for 30 minutes, was injected into the left orbit of a female albino (table 7). In about 11 minutes the width of the lid and pupil of the injected eye increased; after about one hour and a half gradual contraction set in. About 8 minutes after the injection, congestion and swelling of the conjunctiva and lids of the injected eye began; this increased and there were hypersecretion of lacrimal and harderian glands and some protrusion of the eyeball with congestion of the iris, these symptoms being most marked between 25 and 35 minutes after the injection.

The Injection of Normal Horse Serum Into the Orbit of a Sensitized Guinea-Pig.—A male, albino guinea-pig, received 2.5 cc of normal horse serum subcutaneously, and about 3½ months later 0.2 cc of heated horse serum was injected into the left orbit (table 8). There was an immediate closure of the lids and mydriasis caused by reflex action and then widening of the lid and stronger

mydriasis developed, the latter persisting for about 30 minutes, more marked than in the control nonsensitized animal. Similar changes developed about 10 minutes later in the other eye. The congestion and edema were also more marked in this animal than in the control animal. There was a greater hypersecretion of lacrimal and harderian glands in this animal than in the control. There was also marked congestion with hemorrhages of the retinal vessels of the injected eye, more marked than in the fellow eye. There seems to be no doubt that the smooth muscles, blood vessels and eye glands react more markedly to horse serum in the case of the sensitized guinea-pig. After death congestion and hemorrhages of some of the internal organs were discovered, especially in the brain and the retina; there was a noticeably vigorous peristalsis of the intestines.

TABLE 7

RESULTS OF INJECTION OF HEATED HORSE SERUM INTO ORBIT OF NORMAL GUINEA-PIG

Time in Minutes	Lid and Pupil, Widths in Mm.		Remarks
	Left Eye	Right Eye (Control)	
Before injection	5.5 - 3	5.5 - 3	
After injection			
1.5	7 - 4	7 - 4	
2	5.5 - 4	5.5 - 3	
3	5 - 3.5	5 - 2.5	
4	4 - 3	4 - 3	
5	3.5 - 2.5	4 - 3	Left eye:
7	4 - 3	4 - 3	Conjunctival congestion
11	4.5 - 3.5	4 - 3	
15	5 - 3.5	4 - 3	Both lids swollen, chemosis
17	5.5 - 3.75	4 - 3	
20	6 - 4	4 - 3	Marked epiphora
30	7 - 4	5 - 3.5	Changes in eye marked; fundus about normal
40	6.5 - 4	4 - 3	
50	7 - 4	5.5 - 4	
60	7 - 3.75	5.5 - 4	Iris hyperemia
70	6 - 4	5.5 - 4	
80	6 - 4	5.5 - 4	
90	5 - 3.5	4 - 3	Changes in left eye diminishing

At this point the results of some observations on the effect of chloroform may be mentioned briefly: In the beginning of chloroform narcosis of the guinea-pig the lids are closed, but when narcosis is established to excess the lids and pupils become widely dilated; if the narcosis is continued until the animal dies this dilatation persists for some time after death. The only changes observable in the internal organs is a moderate congestion, no hemorrhages being present.

The Effect of Subcutaneous Injection of Salt Solution and Normal Horse Serum in Normal and Sensitized Guinea-Pigs.—The injection of 2.5 cc of 0.9% salt solution subcutaneously on the back was followed in about 10 minutes by a slight narrowing of the lid fissure and of the pupil, the narrowing of the lid fissure increasing a little in the course of the next 30 minutes. These changes were not any greater than those in the control animal handled in the same way but not injected with salt solution. The injection of the same amount of salt solution into a guinea-pig that had received 0.01 cc of normal horse serum intraperitoneally one month before, was followed by an immediate widening of the lid fissure followed by contraction while the pupils remained unchanged; there were no vascular or secretory disturbances.

TABLE 8

RESULTS OF INJECTION OF NORMAL HORSE SERUM INTO ORBIT OF SENSITIZED GUINEA-PIG

Time in Minutes	Lid and Pupil, Widths in Mm.		Remarks
	Left Eye	Right Eye (Control)	
Before injection	6 - 2.5	6 - 2.5	
After injection			
2	4 - 3	4 - 3	
4	5 - 3.5	4 - 3	Pericorneal injection begins at left eye
5	5 - 2.5	4 - 3	Left eyelids and conjunctiva begin to swell; sneezing and weeping
6	5 - 4	4 - 3	
7	5 - 4	5 - 4	Left conjunctival congestion increasing; ear lobes congested; violent muscular movements
8	5 - 3.5	4 - 3	
10	5 - 4	5 - 4	Both eyes and ears congested
13	5 - 4	5 - 4	Left iris and fundus congested strongly
15	5 - 4	5 - 4	Marked pericorneal injection and whitish discharge
20	5 - 3.5	5 - 3.5	Dyspnea
25	5 - 4	5 - 4	Retinal hemorrhages at left eye
30	5.5 - 3.5	5 - 3	Chloroform inhalation
40			Slow respiration, unconsciousness
60			
180	5.5 - 5	5.5 - 4.5	

TABLE 9

RESULTS OF SUBCUTANEOUS INJECTION OF NORMAL HORSE SERUM IN SENSITIZED GUINEA-PIGS

Time in Minutes	Lid and Pupil, Widths in Mm.		Remarks
	Left Eye	Right Eye (Control)	
(Before)	6.5 - 3.5	6.5 - 3.5	
3	6 - 4	6 - 4	Scratching of nose
5	6 - 4	6 - 4	Symptoms of asphyxia
7	5 - 4	5 - 4	
10	5 - 3.75	5 - 3.75	Congestion of conjunctiva, ears, and nose
15	4.5 - 3	4.5 - 3	Epiphora marked, iris hyperemic
20	4.5 - 3	4.5 - 3	Fundus congested
22	4 - 2	4 - 2	
25-30	4 - 2.5	4 - 2.5	
32-40	4 - 3	4 - 3	
42	3 - 2	3 - 2	
45	3 - 2.5	3 - 2.5	
47-48	3 - 2	3 - 2	
49-50	4 - 2	4 - 2	
51	2.5 - 2	2.5 - 2	
52-55	3 - 2	3 - 2	
57-71	3 - 2.5	3 - 2.5	
75	2 - 2.5	2 - 2.5	
77	3 - 2.5	3 - 2.5	
80	2.5 - 2.5	2.5 - 2.5	
82	4.5 - 2.5	4.5 - 2.5	
85	4 - 3	4 - 3	
90	3 - 2.5	3 - 2.5	
97	3.5 - 2	3.5 - 2	
100	3 - 2	3 - 2	
105	4 - 3.5	4 - 3.5	
110	3 - 3	3 - 3	
115	3 - 2.5	3 - 2.5	
120	3.5 - 2.5	3.5 - 2.5	
150	4 - 3.5	4 - 3.5	

The injection of 2.5 cc normal horse serum subcutaneously on the back into albino guinea-pigs did not cause any changes in the condition of the lid fissure or pupil until about 5 minutes later when there was contraction of both lasting for over 2½ hours; at the same time there was some congestion of the conjunctiva, ear lobes, nose and nails. In about 10 minutes tears began to flow; hypersecretion lasted about as long as the congestion, namely, 50 minutes. The fundus showed congestion 30 minutes after the injection. There was some increase in the frequency of respiration and also in the rectal temperature. This shows that normal horse serum subcutaneously in the dose of 2.5 cc, causes definite changes in the eyes—contraction of the lid fissure and pupil, and congestion in the fundus.

A female albino guinea-pig was injected intraperitoneally with 0.01 cc of normal horse serum and 26 days later 2.5 cc of normal horse serum were injected subcutaneously (table 9); respiratory difficulty and general nervous symptoms soon followed; there was some eversion of the lids and marked mydriasis, lasting for about 10 minutes, whereupon an increasing contraction of the lids and pupils developed with congestion of the conjunctiva, lacrimation, and congestion of the iris and fundus. There was a moderate fall in the rectal temperature. The eversion of the lids noted in this experiment, the marked mydriasis, the primary lid contraction, and mydriasis followed by narrowing of lid and pupil would appear to be definite anaphylactic eye phenomena.

TABLE 10
RESULTS OF INTRAVENOUS INJECTION OF HORSE SERUM INTO NORMAL GUINEA-PIGS

Time in Minutes	Lid and Pupil, Widths in Mm.			
	Injected Guinea-Pig		Control Guinea-Pig	
	Right Eye	Left Eye	Right Eye	Left Eye
(Before)	5.5 - 3.75	5.5 - 3.75	5.5 - 3.75	5.5 - 3.75
10				
15	4.5 - 3.75	4.5 - 3.75	5.5 - 3.75	5.5 - 3.75
30	4.5 - 3.75	4.5 - 3.75	5.5 - 3.75	5.5 - 3.75
40	4 - 3.25	4 - 3.25	5.5 - 3.75	5.5 - 3.75
50	5.5 - 3.75	5.5 - 3.75	5.5 - 3.75	5.5 - 3.75
60	5.5 - 3.75	5.5 - 3.75	5.5 - 3.75	5.5 - 3.75
90	5.5 - 3.75	5.5 - 3.75	5.5 - 3.75	5.5 - 3.75
120	5.5 - 3.75	5.5 - 3.75	5.5 - 3.75	5.5 - 3.75

The Effect of Intravenous Injection of Salt Solution in Normal and Sensitized Guinea-Pigs.—The intrajugular injection of 2.5 cc of a 0.9% salt solution was followed by a slight narrowing of the lid fissures and contraction of the pupil within 30 minutes, as compared with the control animal; there was also some diminution in the respiratory frequency and the rectal temperature in the injected animals, but there were no changes in the interior of the eye. Practically the identical changes took place in a guinea-pig previously sensitized with horse serum and then injected with 2.5 cc of salt solution.

Intravenous Injection of Normal Horse Serum Into Normal and Sensitized Guinea-Pigs.—The intravenous injection of 2.5 cc of normal horse serum into a normal guinea-pig was followed by a moderate contraction of the lids and pupil reaching its maximum about 40 minutes after the injection, slight congestion of the conjunctiva, iris, and fundus with lacrimation. Though some lessening in respiratory frequency and in the rectal temperature was noticed soon after the injection, it passed away before long (table 10).

A female, pigmented guinea-pig was injected intraperitoneally with 0.01 c c of normal horse serum and about 40 days later 2.5 c c of normal horse serum were injected into the jugular vein (table 11). In this case a typical anaphylactic death with convulsions took place 4 minutes after the second injection, associated with a marked mydriasis and widening of the lids but followed in 6 minutes after death by contraction, reaching maximum in 40 minutes. In a second similar experiment, in which 2 c c of normal horse serum were injected intravenously into an animal sensitized in the same way, the results were practically the same, postmortem myosis beginning in 6 minutes and reaching maximum in one hour.

TABLE 11
EYE PHENOMENA IN SUDDEN ANAPHYLACTIC DEATH

Time in Minutes	Lid and Pupil, Widths in Mm.					
	1			2		
	Right Eye	Left Eye	Remarks	Right Eye	Left Eye	Remarks
(Before)	6 - 3.75	6 - 3.75		6 - 3	6 - 3	
2	6 - 3.75	6 - 3.75	Convulsions	6.5 - 4	6.5 - 4	Convulsions
4	6 - 4.5	6 - 4.5	Optic disk pale; death	6.5 - 4	6.5 - 4	Optic disk pale; death
After death						
1	6.5 - 5	6.5 - 5				
6	6 - 3.5	6 - 3.5		5.5 - 3	5.5 - 3	
11	5.5 - 2.5	5.5 - 2.5				
13				5.5 - 2	5.5 - 2	
18				5.5 - 2	5.5 - 2	
26	5.5 - 2.25	5.5 - 2.25	Optic disks pale	4.5 - 2	4.5 - 2	Optic disks pale
36	4.5 - 2.25	5 - 2		4.5 - 2	4.5 - 2	
46	4 - 1.75	5 - 1.5		4.5 - 2.25	4.5 - 2	
60	4 - 1.75	4 - 1.5		4.5 - 2	4.5 - 1.5	
105				3.5 - 1.75	3.5 - 1.5	
120	5 - 1.75	4 - 1.5				
225				3 - 1.75	3 - 1.75	
300				2 - 1.75	2 - 1.75	

TABLE 12
EYE PHENOMENA IN ACUTE ANAPHYLACTIC SHOCK

Time in Minutes	Lid and Pupil, Widths in Mm.		Remarks
	Right Eye	Left Eye	
(Before)	4.75 - 3	4.15 - 3	
5	5.5 - 5	5.5 - 5	Convulsions
1	5.5 - 5	5.5 - 5	
13	5 - 5	5 - 5	Congestion of conjunctiva and eye in general. Some relaxation
			Lacrimation
15	4 - 5	4 - 5	
20	4 - 5	4 - 5	
30	4 - 5	4 - 5	
35	4 - 5	4 - 5	
40	4 - 2	4 - 2	Muscular power returning
50	4 - 3.5	4 - 3.5	
60	3 - 3	3 - 3	
80	3 - 4	3 - 4	
After death from chloroform:			
2	2 - 5	2 - 5	
5	4 - 4	4 - 4	
10	4 - 5	4 - 5	

In the case of a guinea-pig injected 4 months before with diphtheria toxin-antitoxin, the intrajugular injection of 2.5 cc of normal horse serum was followed by an acute but nonfatal typical anaphylactic shock with characteristic respiratory symptoms, loss of reflexes, fall of rectal temperature, etc., and the following notable eye phenomena: beginning almost immediately after the injection a marked dilatation of the lid fissure and pupil of both eyes was noted, the lid fissures beginning to contract in 15 minutes and the pupils in 40. Conjunctival congestion, lacrimation, and hyperemia of the iris and fundus developed. The widening of the lid fissures and pupils might have been the result in part of the accompanying asphyxia, and control experiments were made (table 12): A male, albino guinea-pig was choked rapidly by pressure on isolated windpipe, immediately after the intravenous injection of 2.5 cc of normal horse serum, and a normal female pigmented guinea-pig choked similarly but slowly without any injection. In both instances, the lid dilated and strong mydriasis developed and persisted long after death (table 13).

TABLE 13
THE RESULTS OF MECHANICAL ASPHYXIA IN NORMAL GUINEA-PIGS

Time in Minutes	Lid and Pupil, Widths in Mm.					
	Normal Guinea-Pig			Injected Intravenously with Horse Serum		
	Right Eye	Left Eye	Remarks	Right Eye	Left Eye	Remarks
(Before)	6 - 4	6 - 4		6.5 - 3.5	6.5 - 3.5	Daylight
(Before)				6 - 3.75	6 - 3.75	Electric light
2	6 - 5.5	6 - 5.5		6.5 - 4	6.5 - 4	
4						No congestion of the eyes
5	6 - 5.5	6 - 5.5	Retina congested			
15			No congestion at any time of conjunctiva			
21	5 - 5.5	5 - 5.5	Retinal congestion marked			
22	5 - 5.5	5 - 5.5				
After death						Retina pale
3	4 - 5.5	4 - 5.5		6.5 - 4	6.5 - 4	
5						
6	5 - 5.5	5 - 5.5		5.5 - 4	5.5 - 4	
8						
12	5 - 5.5	5 - 5.5		5.5 - 5.5	5.5 - 5.5	
18						
26	5 - 5.5	5 - 5.5		5.5 - 5.5	5.5 - 5.5	
28				5 - 5.5	5 - 5.5	
36	5 - 5.5	5 - 5.5		5 - 5.5	5 - 5.5	
38						
60				4.5 - 5.5	4.5 - 5.5	
120				4 - 5.5	4 - 5.5	

When the postmortal states of the lids and pupils in both experiments of anaphylactic sudden deaths (tables 11 and 12) are compared with the following mechanical asphyxia, a strong myosis (1.5 mm. in 46 minutes to 1 hour) seems to be a characteristic feature of anaphylactic death.

Mydriatics and myotics have no influence on the postmortal state of the pupil, causing no characteristic effects usually, adrenalin

being the only exception to this general rule. V. Szily and Arisawa⁴ observed a pupil contraction in the rabbit after previous injection with fowl or sheep serum into vitreous chamber and 4 weeks later intravenous injection of 5 c c of homologous serum. The pupil contraction was brief and limited to the treated eye only. They give no explanation of the mechanisms. Woods⁵ noted contraction of the pupil in the dog when previously sensitized with uveal tissue and later perfused with oxygenated normal defibrinated dog serum containing that specific antigen. Neither author seems to have observed any anaphylactic lid phenomenon or primary dilatation of the pupil as part of the reactions of anaphylaxis.

According to Schultz's¹ work on excised blood vessels, it would be expected that a vasoconstrictive action would result in anaphylaxis, but my experiments indicate, on the contrary, a vasodilating action on the tissues of the eye and adnexa, on the earlobes, nose and nails. Comparison of the lesions of anaphylactic shock and of pure mechanical asphyxia indicates that the well-known visceral congestion and hemorrhages in these conditions are due both to indirect asphyxial and direct anaphylactic action on blood vessels. This affirmation of an anaphylactic vasodilating action is supported by Frölich's⁶ experiments on the peritoneum of sensitized frogs.

SUMMARY AND CONCLUSIONS

Generally speaking, the immediate effect of the application of horse serum applied to the eye of normal and of sensitized guinea-pigs is dilatation of the lid and pupil succeeded by contraction. In the sensitized animal, however, the response is more prompt and vigorous.

The primary dilatation would seem to be the result of stimulation of the tarsal smooth muscles of the lid and the dilator smooth muscle of the iris. In cases of anaphylactic shock the eye phenomena mentioned may be increased as a result of the asphyxia and other general effects.

The secondary narrowing of the lid fissure and contraction of the pupil may be explained as due to the loss of the tonus of the tarsal muscle and of the dilator pupillae on the one hand and to the contraction of the sphincter muscle of the iris associated with congestion on the other hand. The primary stimulation of the tarsal and dilator muscles

⁴ Die Anaphylaxie in d. Augenheilk., 1914, pp. 139 and 149.

⁵ Studies of Musser Dept. of Research Med., 1916-1918, 4, pp. 13 and 14.

⁶ Ztschr. f. Immunitätsf., 1914, 20, p. 476.

may result from very small doses of the active principle concerned and may pass easily into a state of exhaustion from overstimulation. The stimulation of the sphincter of the pupil requires a stronger action. The primary and secondary effects on the smooth muscles of the lid and iris of guinea-pigs suggest that the anaphylactic action involves the ends of both the true and parasympathetic nerve fibers on both sets of plain muscles in the lid and the iris.

In addition to these phenomena, anaphylactic intoxication with horse serum may be associated with more or less well marked circulatory disturbances with edema and congestion of lid, conjunctiva, iris and ocular fundus, hemorrhages of epibulbar and retinal vessels. The direct application to the eye of horse serum, heated or unheated, may cause vascular dilatation in the normal, but hemorrhage is observed, especially in the sensitized guinea-pigs, and this effect may be obtained independently of asphyxia; hence it is due to direct action on the vessels.

In the normal and sensitized guinea-pig horse serum may cause hypersecretion of the lacrimal and harderian glands, especially on local application in the sensitized animal; this effect may be the result of the hyperemia, but direct stimulation of the glands and their nerves is not excluded.

In addition to the characteristic postmortem appearances of anaphylactic shock, seen especially in the dilatation of the lungs, congestion and hemorrhagic extravasation, we have also to make special note of a rapid and strong contraction of the pupil after anaphylactic death.

As all the anaphylactic eye phenomena—stimulation of plain muscles, circulatory disturbances and hypersecretion of eye glands—appear to be an intensification of the reaction that follows the application of horse serum to the normal eye, it may be assumed that the normal guinea-pig possesses small quantities of the antisubstances necessary for the anaphylactic reaction.